



NOTES

HUMORAL & B-CELL DEFICIENCIES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Ineffective B-cell function → impaired antibody production, cellular immunity intact → recurrent, severe upper/lower respiratory tract infections, encapsulated bacteria

CAUSES

- Familial/sporadic, specific mutations

SIGNS & SYMPTOMS

- Mostly asymptomatic
- Infections, recurrent fever, autoimmune diseases, allergic reactions, chronic diarrhea, hepatosplenomegaly, failure to thrive (FTT)

DIAGNOSIS

LAB RESULTS

- Evaluate levels of immunoglobulins (Ig), specific antibodies, B-cells

OTHER DIAGNOSTICS

- Clinical presentation

TREATMENT

OTHER INTERVENTIONS

- Replacement of Ig

VISIT...

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COMMON VARIABLE IMMUNODEFICIENCY

osms.it/common-variable-immunodeficiency

PATHOLOGY & CAUSES

- Immune disorder characterized by hypogammaglobulinemia
 - IgG, IgM, IgA; inherited/sporadic
- Defect in **B-cell differentiation** → impaired lymphocyte activation, function

CAUSES

- Unclear
- Intrinsic defects in B-cells → antibody deficiency
 - Impaired T-cell mediated activation
 - Impaired differentiation into plasma cells → ↓ immunoglobulins
- Mutations in genes encoding B-cell activating factor (BAFF) cytokine receptor/inducible costimulator (ICOS)

COMPLICATIONS

- **Autoimmune disorders**
 - Rheumatoid arthritis, autoimmune hemolytic anemia (AHA)
- **Lymphoid malignancy**, gastric cancer
- **Bronchiectasis** secondary to recurrent infections
- Granulomatous infiltration
- Poor immune response to immunizations

SIGNS & SYMPTOMS

- **Usually presents > two years old**
- Variable presentation secondary to antibody deficiencies → recurrent infections (e.g. sinopulmonary pyogenic, meningoencephalitis)

DIAGNOSIS

LAB RESULTS

- Decreased serum IgG levels, marked decrease in IgM/IgA
- Lack of antibody immune response to protein antigens/immunization
- Genetic testing for mutations

OTHER DIAGNOSTICS

- > four years old
- History of recurrent infections, positive family history
- Physical examination
 - Peripheral lymphadenopathy
- Exclusion of other causes of hypogammaglobulinemia (e.g. X-linked agammaglobulinemia)

TREATMENT

MEDICATIONS

- Immunosuppressants to control autoimmune clinical features
- Antibiotics to treat chronic lung infections

OTHER INTERVENTIONS

- Ig replacement therapy

HYPER IGM SYNDROME

osms.it/hyper-IgM-syndrome

PATHOLOGY & CAUSES

- Immune disorder; elevated levels of IgM; low to absent IgG, IgA, IgE
 - X-linked/autosomal recessive
- Defect in B-cell antibody class switching → defective lymphocyte activation, function
- Predisposition to certain infections
- IgM antibodies can react with blood cells → autoimmune hemolytic anemia, thrombocytopenia, neutropenia
- In elderly, proliferation of plasma cells producing IgM can infiltrate gastrointestinal (GI) tract mucosa

CAUSES

- Genetic defects
 - **Type 1 (most common):** X-linked disease of CD40 ligand (CD40L) gene → affects T cell ability to stimulate, activate B cells
 - **Other subtypes:** affect class switching, autosomal recessive diseases

SIGNS & SYMPTOMS

- Recurrent severe **pyogenic/opportunistic** infections early in life
- Related to cause of infection
 - **Fungi:** *Pneumocystis jiroveci* → pneumonia
 - **Protozoa:** *Cryptosporidium* → infects biliary tract → diarrhea, malabsorption
 - **Viruses:** *Cytomegalovirus* (CMV) → viral pneumonia/hepatitis
 - **Encapsulated bacteria:** *Streptococcus pneumoniae* → otitis media, sinusitis, bacterial pneumonia

DIAGNOSIS

LAB RESULTS

- No serum IgA, IgE, extremely low IgG
- Normal/elevated IgM
- Flow cytometry/genetic test
 - Confirm mutation in CD40L

OTHER DIAGNOSTICS

- History of recurrent infections, positive family history

TREATMENT

MEDICATIONS

- Prophylactic treatment with trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci*

OTHER INTERVENTIONS

- Ig replacement therapy
- Individuals with persistent neutropenia may require granulocyte colony stimulating factor (G-CSF)
- Hematopoietic stem cell transplantation (HSCT) → bone marrow transplant (BMT)/cord blood stem cell transplant

HYPERIMMUNOGLOBULIN E SYNDROME

osms.it/hyper-IgE-syndrome

PATHOLOGY & CAUSES

- Rare immunodeficiency; recurrent skin, respiratory infections, eczema, elevated serum IgE levels
- AKA Job syndrome
- Mostly sporadic

TYPES

Autosomal dominant (AD-HIES)

- More common

Autosomal recessive (AR-HIES)

- Increased risk of developing fatal complications, infections, malignancies, autoimmune disorders

SIGNS & SYMPTOMS

- Primary characteristics
 - **Newborn rash/eczema**, first manifestation; impetigo, boils
 - **Recurrent staphylococcal skin abscesses**, without typical signs of inflammation ("cold abscesses")
 - **Recurrent respiratory infections** → formation of lung cavities, pneumatoceles
- Ear, sinus infections; mucocutaneous candidiasis; facial, skeletal findings (e.g. hyperextensibility of joints, retained primary teeth, due to connective tissue, skeletal abnormalities); susceptibility to malignancies (esp. lymphomas), autoimmune diseases

DIAGNOSIS

LAB RESULTS

- Markedly elevated serum IgE levels

OTHER DIAGNOSTICS

- Clinical presentation

TREATMENT

MEDICATIONS

- Prophylactic administration of trimethoprim-sulfamethoxazole
- Limited use of steroids for eczema

SURGERY

- Incision, drainage for skin/lung abscesses

OTHER INTERVENTIONS

- Skin care, antisepsis (prevent infections); prompt treatment of skin, respiratory infections; control of pulmonary complications; moisturizing creams
- HSCT

IGG SUBCLASS DEFICIENCY

osms.it/IgG-subclass-deficiency

PATHOLOGY & CAUSES

- Decrease in serum concentration of $\geq$ one subclasses of IgG
 - IgG1, IgG2, IgG3, IgG4 while total IgG concentration remains unchanged
 - IgG1 accounts for 60–70% of total IgG; IgG1 deficiency presents with low total IgG
 - IgG2/IgG3 deficiencies most common
 - Low IgG4 alone insufficient evidence of antibody deficiency disorder
- IgG subclass deficiency
 - Integral component of other primary immunodeficiency diseases (e.g. Wiskott–Aldrich syndrome)
- Individuals with IgG subclass deficiency have **recurrent ear/sinus/lung infections**
- In many children, deficiency resolves with age
- May develop into common variable immunodeficiency (CVID)

SIGNS & SYMPTOMS

- Mostly asymptomatic
- Recurrent ear/sinus/pulmonary infections with **encapsulated bacteria** (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*)
- Increased incidence of atopic disease, chronic airway disease, autoimmune disease (e.g. vasculitis)

DIAGNOSIS

LAB RESULTS

- $\geq$ one low IgG subclasses with normal total IgG
- History of recurrent sinopulmonary infections
- Inadequate response to vaccination

TREATMENT

MEDICATIONS

- Antibiotic prophylaxis

OTHER INTERVENTIONS

- Treatment of conditions predisposing to recurrent infections (e.g. asthma)
- Immunization with conjugate vaccines
- Long-term Ig replacement therapy

ISOLATED PRIMARY IMMUNOGLOBULIN M DEFICIENCY

osms.it/isolated-primary-IgM-deficiency

PATHOLOGY & CAUSES

- Rare immune disorder; decreased IgM antibodies in bloodstream
- AKA selective IgM immunodeficiency (SIgMD)
- Unclear etiology
 - Rapid degradation of B cells after being secreted
 - B cells unable to mature, produce free IgM
- Associated with recurrent infections, allergic conditions, Bloom's syndrome, celiac disease, systemic lupus erythematosus (SLE), malignancy

COMPLICATIONS

- Infections may progress to meningitis, sepsis

SIGNS & SYMPTOMS

- Start in infancy, vary widely
 - May be asymptomatic; recurrent severe infection (e.g. sinusitis, diarrhea, skin infections); allergic reactions (e.g. atopic dermatitis)

DIAGNOSIS

LAB RESULTS

- Decreased levels of IgM antibodies

OTHER DIAGNOSTICS

- History of recurrent infections

TREATMENT

MEDICATIONS

- Prophylactic antibiotics for severe recurrent infections
- Antibiotics to treat infections

SELECTIVE IMMUNOGLOBULIN A DEFICIENCY

osms.it/selective-IgA-deficiency

PATHOLOGY & CAUSES

- Most common primary immunodeficiency; isolated deficiency of IgA in blood, secretions
- IgA deficiency (primarily in mucosal surface secretions) → infections, GI disorders, autoimmune diseases, allergic reactions
- Unknown etiology; associated with several non-causative genetic alterations

RISK FACTORS

- Family history of IgA deficiency/CVID

SIGNS & SYMPTOMS

- May be asymptomatic; may present significant clinical problems (less common)
- Susceptibility to infections (e.g. sinopulmonary, ear infections)
- Autoimmune diseases
 - Rheumatoid arthritis, systemic lupus erythematosus, immune thrombocytopenic purpura
- GI disorders (e.g. diarrhea); *Giardia lamblia* infections
- Allergic disorders (e.g. asthma)
- Anaphylactic reactions to blood products

DIAGNOSIS

LAB RESULTS

- Individual > four years old
 - Undetectable levels of IgA

OTHER DIAGNOSTICS

- Clinical presentation
- Exclude other causes of hypogammaglobulinemia, IgA deficiency secondary to medications

TREATMENT

MEDICATIONS

- Antibiotics to treat infections/long-term antibiotic prophylaxis to prevent them
- Anti-inflammatory drugs, steroids, monoclonal antibodies for autoimmune diseases
- Antihistamines, anti-inflammatory drugs, steroids for allergies

TRANSIENT HYPOGAMMAGLOBULINEMIA OF INFANCY

osms.it/infant/hypogammaglobulinemia

PATHOLOGY & CAUSES

- Temporary decrease in circulating Ig during first months of life
 - Maternal IgG pass fetus through placenta in sixth month of pregnancy → maternal IgG slowly diminishes, disappears six months after birth
 - By 3–6 months of age, healthy infants begin making IgG as maternal IgG levels fall
 - If severe/prolonged beyond six months of age → THI
- More common in individuals who are biologically male (2:1)
- Most individuals with THI have adequate antibody responses to infections/immunizations → usually not susceptible to infections
- Serum Ig levels should return by age four years, may persist for few more years
- Severe, life-threatening infections rare

SIGNS & SYMPTOMS

- Usually asymptomatic
- Recurrent infections
 - Upper respiratory, ear, sinus
- Atopic manifestations
 - Asthma, eczema, food allergy
- GI difficulties

DIAGNOSIS

LAB RESULTS

- IgG level < two standard deviations below age-appropriate mean, with/without diminished levels of other serum Ig, on at least two occasions
- Ig must normalize during childhood/rarely during adolescence

OTHER DIAGNOSTICS

- Diagnosis of exclusion; other permanent forms of hypogammaglobulinemia must be excluded first

TREATMENT

MEDICATIONS

- Antibiotics
 - If persistent infections occur

OTHER INTERVENTIONS

- Immunoglobulin replacement therapy if infections severe/persistent

WISKOTT–ALDRICH SYNDROME

osms.it/wiskott-aldrich_syndrome

PATHOLOGY & CAUSES

- Rare syndrome; classic triad of microthrombocytopenia, eczema, recurrent pyogenic infections
- AKA eczema-thrombocytopenia-immunodeficiency syndrome
- X-linked recessive inheritance pattern; can also result from spontaneous DNA mutation affecting hematopoietic cells
- Most commonly presents in individuals who are male, > two years old
- Progressive loss of T lymphocytes in peripheral blood, lymph nodes → impairment of T-cell mediated, humoral immunity

CAUSES

- Mutation in **Wiskott–Aldrich syndrome protein (WASP) gene** at Xp11.23
 - Encodes for hematopoietic cellular proteins involved in cytoskeletal architecture

COMPLICATIONS

- Increased risk of infections, bleeding, autoimmune disease, malignancy

SIGNS & SYMPTOMS

- **Thrombocytopenia** → petechiae, bruising, epistaxis, severe bleeding
- **Eczema**, atopic symptoms
- **Recurrent sinopulmonary/opportunistic infections** caused by
 - Encapsulated bacteria (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*)
 - Fungi (e.g. *Pneumocystis jirovecii*, *Candida albicans*)
 - Viruses (e.g. molluscum contagiosum, varicella zoster, cytomegalovirus)

DIAGNOSIS

LAB RESULTS

- Low to normal IgG, IgM
- High IgA, IgE
- Decreased number, function of T cells
- Peripheral blood smear
 - Fewer, smaller platelets secondary to cytoskeletal remodeling
- Genomic DNA sequencing
- Flow-cytometry
 - Screening test, determine presence of WASP

OTHER DIAGNOSTICS

- History of bleeding, recurrent infections, eczema
- Clinical presentation, positive family history

TREATMENT

MEDICATIONS

- Prophylactic antimicrobials
- IVIG for recurrent infections

SURGERY

- Splenectomy for severely low platelets

OTHER INTERVENTIONS

- Platelet transfusions for severely low platelets
- Blood transfusions for severe bleeding
- HSCT
 - Potentially curative

X-LINKED AGAMMAGLOBULINEMIA

osms.it/x-linked_agammaglobulinemia

PATHOLOGY & CAUSES

- Immunodeficiency disorder; severe hypogammaglobulinemia, deficiency of all classes of antibodies → increased susceptibility to infection
- AKA Bruton's disease
- Familial/sporadic **mutation in BTK gene on X-chromosome** → X-linked recessive genetic condition
 - Manifests as disease in individuals who are biologically male
 - Individuals who are biologically female only carriers
- Ineffective Bruton's tyrosine kinase (BTK) enzyme → B-lymphocyte precursors fail to mature into B lymphocytes, plasma cells → **differentiation stops at pre-B cell stage** → absence of B-cells in circulation → deficiencies of all Ig → high risk of developing infections
 - Bacterial (e.g. acute/chronic pharyngitis, sinusitis, otitis media, bronchitis, pneumonia), viral (e.g. enteroviruses, polio, coxsackievirus), protozoal intestinal parasitosis (e.g. giardia lamblia)
- T-cell mediated immunity remains intact; some viral, fungal, protozoal infections still cleared

SIGNS & SYMPTOMS

- Newborns typically asymptomatic; **after six months** transplacentally-delivered Ig no longer present → prone to develop infections
- **Infections frequently occur** at mucous membranes, can also involve bloodstream, spread to internal organs, bones, joints, brain (e.g. otitis media, pharyngitis, bronchitis)
- **Small/absent tonsils, lymph nodes**

DIAGNOSIS

LAB RESULTS

- Serum Ig levels
 - **All Ig markedly reduced/absent**
- Number of B-cells in peripheral blood
 - **Nearly absent** (most characteristic finding)

OTHER INTERVENTIONS

- Clinical presentation
 - Any child with recurrent/severe bacterial infections
- Genetic testing
 - Absence of BTK protein/presence of BTK mutation

TREATMENT

OTHER INTERVENTIONS

- Lifelong IVIG can be given to replace missing Ig
- Complete, prompt treatment of infections
- **Avoid live viral vaccines** (e.g. polio vaccine)